Guidance for Industry

Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Clinical

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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This document has been developed to provide guidance in the design, conduct, and evaluation of clinical studies to assess the effects of orally inhaled and intranasal corticosteroids on linear growth. This guidance is intended to provide recommendations for sponsors of orally inhaled and intranasal corticosteroids on study design and efficacy and safety issues for (1) approved drug products whose treatment effect on prepubescent growth has not been adequately characterized and (2) potential new drug products that could be used in the treatment of allergic rhinitis and/or asthma in children. This guidance does not address study designs for comparison of active moieties or for two different products containing the same active moiety.

Recommendations provided in this guidance are based on an in-depth review of issues raised by pediatric growth studies previously conducted with orally inhaled and intranasal corticosteroids. The importance of these studies is reflected in the observation that changes in growth velocity are indicative of systemic corticosteroid effects, and many long-term adverse consequences of systemic activity cannot be readily measured. An estimate of the growth effect of a drug, while important by itself, should also be considered an important sentinel of unmeasured systemic effects that can therefore provide additional safety information.

It should be noted that the recommendations for pediatric growth studies contained in this guidance reflect normative growth data gathered from healthy children in a U.S. population. Sponsors planning to conduct international studies should take this into consideration and are strongly encouraged to contact DPADP for further guidance prior to the initiation of such trials. Although recommendations on patient selection, relevant inclusion/exclusion criteria, choice of primary and secondary endpoints, statistical analysis, and safety monitoring are not binding or mandatory for

[1] This guidance has been prepared by the Division of Pulmonary and Allergy Drug Products (DPADP), the Division of Metabolic and Endocrine Drug Products (DMEDP), and the Division of Biometrics II (DBII) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

drug approval, sponsors are strongly encouraged to discuss details of study design and specific issues relating to individual drug products with the review division before conducting clinical trials that estimate growth effects.

II. BACKGROUND

New information regarding the potential adverse effects of inhaled and intranasal corticosteroids on growth rates in children has become available in the past few years. Correspondingly, the experience of both industry and FDA in the design, execution, and evaluation of growth studies in children has been markedly enhanced. Studies recently submitted to the Agency have demonstrated reduced growth velocities that were statistically significant (in the range of approximately 1 centimenter (cm) per year) among active treatment groups exposed to inhaled or intranasal corticosteroids as compared to control groups (placebo or noncorticosteroid asthma treatments such as beta-agonists). Several different active corticosteroid moieties have demonstrated this effect. The recommendations in this guidance are specifically applicable to intranasal and orally inhaled corticosteroids; however, many of the recommendations can be extended to include evaluation of possible growth effects with other therapies for asthma and allergic rhinitis.

Because the clinical relevance of the differences in prepubescent growth velocities on final adult height (as estimated by 1-year trials) is yet unknown, a *clinically meaningful difference* of 1-year growth velocities between treatment groups is difficult to define. Therefore, the growth study recommendations described in this document do not fit into the usual framework of a superiority, inferiority, or equivalence study. Rather, the objective of these growth studies is to characterize, as well as possible, the estimate of the difference in prepubescent growth velocities between treatment with an active moiety and a control group. The sample size of the study should be based on the desired precision (width of a 95% confidence interval) for the treatment effect.

Growth studies the Agency has previously reviewed have varied greatly in their designs. While some studies have tended to focus on the question of potential differences in growth rates between treatment regimens that represent how children are actually treated in clinical practice, this approach has led to the introduction of confounders that limited the interpretation of the studies' results. Specifically, some studies allowed for one or more of the following practices: titration of corticosteroid dose, generous use of oral corticosteroids as rescue medication, and inclusion of older children who could potentially enter the pubertal growth spurt during the trial. Measurement error and missing data further complicated the analyses and results. The study design considerations suggested by this guidance are not intended to reproduce actual clinical practice. Rather, this guidance outlines characteristics of study designs that can reduce the variability and/or potential bias of the estimates of differences in growth velocity between treatment groups.

Sponsors of both intranasal and inhaled corticosteroid products that contain the same active moiety may be able to use pharmacokinetic data to bridge the growth findings associated with one formulation to a second formulation. Further consultation with the review division is recommended during the design of a bridging program.

III. GENERAL STUDY DESIGN RECOMMENDATIONS FOR GROWTH STUDIES

The following are general recommendations on designing growth studies in children with asthma and/or allergic rhinitis. However, it is important to point out that there are differences with regard to the comparator or control group selected for the two indications. It is generally accepted that placebo-controlled studies can be ethically performed for the indication of allergic rhinitis. Thus, for children with allergic rhinitis, a placebo control group is recommended. For children with mild, persistent asthma, the control arm should include clinically appropriate, noncorticosteroid medication consistent with published guidelines in addition to the use of a drug product dummy (NIH pub no 97-4051, *NAEPP Guidelines for the Diagnosis and Management of Asthma 1997*).

- For both the orally inhaled and the intranasal corticosteroids, assessment of growth effects should be based on adequate and well-controlled phase 3 or 4, double-blind, controlled, parallel group clinical trials. There should be a single-blind (patient-blinded) baseline period to assess baseline growth velocity. There should also be a follow-up period (preferably using a single-blind placebo or noncorticosteroid medication, as described above) to assess potential *catch-up* growth. The duration of the baseline period should be at least 16 weeks, the treatment period should be at least 48 weeks, and the follow-up period should be at least 8 weeks. Use of stadiometer data from office visits prior to randomization as baseline data in lieu of the baseline period may, under some circumstances, be appropriate. However, the sponsor is encouraged to consult with the reviewing division concerning the recommendation of this approach because of its potential to introduce variability into baseline growth velocity estimates.

- Measurements should be made using stadiometry and recorded to the nearest tenth of a centimeter. If the stadiometer has not been calibrated in the previous 4 hours, it should be calibrated immediately prior to measurement of patient height.

- The study design should incorporate practices that reduce measurement error. The investigators or examiners should be trained in stadiometry and calibration procedures. Ideally, the same person should measure the children at every visit and should be blinded to the patients' status in the study (i.e., on-study, receiving double-blind treatment, discontinued, receiving open-label treatment).

- The sponsor should make every effort to obtain growth measurements as planned, irrespective of whether patients discontinue the study medication. The measurements made after the date of discontinuation can be used in a *sensitivity analysis*. Although discontinued patients can take other medications that affect growth, continued measurement is useful for assessing the sensitivity of the analyses and results (see Secondary Analyses below).

- The investigator, examiner, patient, caregiver, and study personnel should remain masked to the study treatment for patients who discontinue because of worsening symptoms, unless unblinding is important for safety or treatment decisions.

- For purposes of growth studies, it is not recommended to recruit children near the time of puberty because of the rapid increase in growth velocity that may occur over a relatively brief period (Tanner and Davies, 1985). Although information concerning growth suppression during the pubertal growth spurt has clinical relevance, the goals of growth studies are, in many respects, pharmacodynamic in nature. To detect a deceleration in growth velocity over the approximate 1-year course of these studies, it is important that the expected growth velocity be relatively constant. This determination will be confounded if a child's growth velocity is undergoing the normal physiologic acceleration associated with puberty. For this reason, prepubertal children are preferred, and the study design should minimize the likelihood of patients entering puberty during the study.

- Tanner staging at baseline and during the treatment period may not identify all patients experiencing a growth spurt associated with puberty. The first measurable sign of puberty in girls can be the beginning of the growth spurt, and it may precede the onset of secondary sexual characteristics by as much as 1 year (*Current Pediatric Diagnosis and Treatment 14th Edition*, 1999, and *Rudolph's Pediatrics 20th Edition*, 1996). There are conflicting statements in the literature about the timing of the growth spurt in boys relative to the onset of secondary sexual characteristics.[2] While randomization may ameliorate this problem, stratified randomization based on age and gender is recommended to help balance the percentage of patients whose pubertal growth spurt may have already begun during the baseline period or will begin during the treatment period.

IV. PROTOCOL DESIGN

A. Inclusion Criteria

Patients included in growth studies with orally inhaled corticosteroid products should have a history of mild, persistent asthma (NIH pub no 97-4051, *NAEPP Guidelines for the Diagnosis and Management of Asthma 1997*) for a minimum of 6 months prior to study entry. Patients should also have a documented percentage predicted $FEV_1 \geq 80$ percent after withholding beta-agonist for ≥ 6 hours at both the screening and first baseline visits. These patients are expected to have a limited need for oral corticosteroid use during the 1-year treatment period.[3] Inclusion criteria may warrant modification if the sponsor is

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[2] *Adolescent Medicine*, 3rd Edition (1997), states that, "The growth spurt [in males] usually begins at stage 3, reaches a peak during stage 4 and is all but complete by stage 5" (p. 13). *Rudolph's Pediatrics*, 20th Edition (1996), section 22.9.1 states that, "the initiation of the adolescent growth spurt precedes the onset of secondary sex characteristics by approximately 1 year in boys and girls."

[3] Patients with mild, persistent asthma are the preferred population for ethical and clinical design reasons (see GENERAL STUDY DESIGN RECOMMENDATIONS FOR GROWTH STUDIES). Children with mild, persistent asthma are unlikely to suffer serious consequences if randomized to noncorticosteroid maintenance therapy but are sufficiently ill to justify potential randomization corticosteroid therapy that may suppress growth. From a design standpoint, children with mild, persistent asthma are expected to have no or limited need for oral corticosteroid use during the 1-year treatment period, and therefore the impact of oral corticosteroid use on analyses of growth velocity will be minimized.

conducting a study of the growth effects of noncorticosteroid drug products to be used in the treatment of asthma.

The patient population for the intranasal products should have a history of persistent allergic rhinitis for a minimum of 2 years prior to study entry with expected symptoms during a majority of the treatment period.

To minimize the potential for patients to reach the onset of puberty during the trial, the inclusion criteria should state that the age of the male subjects will be ≤ 10.5 years and the age of the female subjects will be ≤ 9.5 years at the end of the follow-up period. The sponsor is encouraged to set the upper age limit inclusion criteria as low as feasible to minimize the likelihood of recruiting pubertal children, based on prior recruitment experiences and available normative data for the population under study.

B. Exclusion Criteria

Tanner staging should be performed at the end of each period (baseline, treatment, and follow-up) to help identify pubescent patients. Patients with Tanner stage greater than 1 during the baseline period should be excluded from the treatment period. (Note that if patients become pubescent during the treatment or follow-up periods, they should remain in the trial, performing all visit procedures.)

Other exclusion criteria include:

- Baseline growth velocity less than the 3rd percentile.[4]

- Weight and Body Mass Index less than the 3rd or greater than the 97th percentiles.

- Bone age greater than 1 year different from patient's chronological age. It is strongly recommended that the bone age be determined by a central reader for all patients in the study.[5]

[4] The purpose of this criterion is to exclude patients with growth disorders from studies in which they may receive a growth-inhibiting drug. Baseline growth velocity can be calculated as a difference between the first and last baseline measurements or as a regression line using all the baseline measurements.

[5] Children whose bone age is ≥ 2 years different from their chronological age are considered to be outside of the normal range for this parameter. On this basis, it can be argued that a 1-year upper limit is unduly restrictive and that an upper limit of < 2 years would be more appropriate. Sponsors considering modification of their protocols based on this exclusion criteria are strongly urged to contact DPADP for advice. In particular, the importance of a 2-year difference between bone age and chronological age increases at the extremes of the pre-pubertal age range. A 4-year-old child who has the bone age of a 2-year old is of greater concern than an 8-year old with a bone age of 6 years and is more likely to have baseline growth abnormalities. Similarly, a 9-year-old child with a bone age of 11 years may be about to enter his or her pubertal growth spurt and ideally should not be recruited into a growth study. The importance of a close correlation between bone age and chronological age also increases if a non-U.S. study is contemplated, since normative data based on U.S. children may not apply (see INTRODUCTION).

- Use of inhaled, intranasal or high potency topical corticosteroids within 6 weeks and systemic corticosteroids within 3 months of the first baseline visit.
- Use of corticosteroids by any route of administration likely to have a systemic effect during the baseline period.
- Treatment at any time prior to screening that might influence linear growth, including, but not limited to, methylphenidate hydrochloride, thyroid hormone, growth hormone, anabolic steroids, calcitonin, estrogens, progestins, biphosphonates, anticonvulsants, or phosphate-binding antacids.

C. Assessment of Patient Adherence

The study protocol should specify how adherence to medication use will be determined and documented throughout the trial.

D. Action Plan for Worsening Symptoms

The study protocol should specify the course of action to be taken in the event of worsening asthma or allergic rhinitis and should include the types and doses of allowed rescue medication. For worsening allergic rhinitis, an oral decongestant or antihistamine can be considered. For safety reasons, standard-of-care guidelines should be followed in the management of all acute asthma exacerbations. Asthma management can include repeat doses of beta-agonists and systemic corticosteroids, administered orally or parenterally, at the discretion of the primary investigator. Worsening asthma control that is asymptomatic (e.g., when a patient is found to have a decline from baseline in peak expiratory flow rate or FEV_1) can be managed less intensively. Continued observation with no immediate change in therapy or the addition of (or increase in) an inhaled corticosteroid can be considered reasonable options. In each of these cases, patients should be continued in the study, and the protocol should specify how rescue medication use will be analyzed between the treatment groups. Analyses of outcomes under the various conditions of rescue medication use (dose and duration) should be provided in the clinical trial report (see Secondary Analyses).

E. Dose and Dosage Regimens

Sponsors should include the proposed to-be-marketed or labeled starting pediatric dose of drug in the growth study. Ideally, a range of doses (multiple treatment arms) should be studied if a dose range is approved or proposed in the pediatric population.

F. Data Quality

The protocol should specify the manner in which physiologically improbable data points or sequences of data points will be assessed (i.e., data points that demonstrate a large increase or decrease in height between visits, or a sequence of data points that show a pattern of linear growth for a time, then a sharp increase in height, followed by a decrease and the original linear pattern).

G. Statistical Issues

Although there is general agreement that a decrement in growth velocity over a 1-year period may have clinical relevance, there remains some disagreement about how much change is clinically relevant and what the impact may be on final adult height. Further, regardless of any effect on adult height, growth effects seen in such a trial should be regarded as a sentinel for systemic effects (see INTRODUCTION). Since a *clinically meaningful difference* of growth velocities between treatment groups is difficult to accurately define, interpreting inferential statistical testing may also be difficult. If the sponsor plans to perform statistical tests comparing treatments, the study protocol should contain provisions for the statistical analyses and adjustments for multiple comparisons.

H. Sample Size

As stated above, a *clinically meaningful difference* of growth velocities between treatment groups is difficult to define. Therefore, the sample size of the study should be based on the desired precision (width of a 95% confidence interval) of the estimate of the difference in mean growth velocities between active and control treatments. Mean treatment effects seen in previous growth studies submitted to the Agency have been observed to be 0.5 cm per year and greater. It is desirable that the growth studies provide an estimate of treatment effect with a high level of precision (e.g., total length of 95 percent confidence interval 0.5 cm). This level of precision should be attainable with sample sizes on the order of ≥ 150 completed patients per treatment group, using the design characteristics outlined in this document, and based on an analysis that controls for baseline growth velocity, age, and gender in the model. Sponsors should perform their own sample size calculations based on the expected standard deviation using their planned study design, patient population, and active moiety. Studies with 95 percent confidence intervals considerably wider than 0.5 cm might not be interpretable due to the lack of precision in the estimate of treatment effect.

V. DATA ANALYSIS

A. Primary Analysis

The preferred measure of growth effects is the difference in growth velocity during the treatment period between active and placebo treatments. Individual patient growth velocities during the baseline, treatment, and follow-up periods could be calculated using change from baseline in height or estimated using linear regression models. An ANCOVA model involving all randomized patients with at least three recorded height measurements during the double-blind treatment period is recommended to estimate the mean difference between treatment groups in growth velocity over the treatment period. Appropriate predefined factors and covariates should be used in the model as explanatory variables. A 95 percent confidence interval around the mean difference in growth velocities between the control group and the active treatment group should be constructed.

B. Secondary Analyses

The sponsor should also consider performing the following secondary analyses:

- Subset analysis excluding any patient who exhibited ≥ Tanner Stage 2 characteristics at the end of the treatment period.

- Analysis of the percent of children who are below a certain percentile of growth velocity (e.g., 3rd percentile) or percent of children whose percentile for height decreases during the treatment period.

- Categorical or "shift" analysis showing change in growth velocity percentile for each child from baseline to endpoint (by quartiles, for example).

- Subset analysis excluding children who received "rescue" systemic corticosteroids during the double-blind treatment period.

- Summary of growth velocities during the follow-up period.

- Descriptive comparison of the growth velocities between boys and girls.

- Analyses of efficacy (see Efficacy Variables).

C. Other Safety Variables

All routine laboratory tests (chemistry, hematology, liver function, and urinalysis) should be obtained in study patients at least four times: at screening and at the last visit of each phase of the study (baseline, treatment, and follow-up). Also, assessment of adrenal response using a sensitive test (e.g., through 24-hour urinary free cortisol level measurements, or 24-hour plasma cortisol AUC pretreatment, at study endpoint, and 6 weeks post-study) should be conducted in studies of corticosteroids.

D. Efficacy Variables

Assessment of efficacy variables in these studies would serve to help identify nonadherence and/or poorly controlled asthma or allergic rhinitis. Therefore, for the asthma studies, it is recommended that pulmonary function tests be performed at every office visit. Also, peak flow rates, asthma symptom scores, and use of rescue medication should be recorded in daily diaries. For allergic rhinitis studies, efficacy can be assessed when the following data are used: nasal symptom scores and use of rescue medication recorded in subject diaries. The sponsor should summarize these data for each phase of the study (baseline, treatment, and follow-up periods) for each treatment group.

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